BAY-19-8004

Title:

Pde4 and pde3/4 inhibitors for use in t cachexia

Document Type and Number: United States Application 20060079540

Link to this Page: http://www.freepatentsonline.com/20060079540.html

Abstract: The invention relates to the use of a PDE4 or PDE3/4 inhibitor for

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Application Number:	535815
Filing Date:	2003-11-26
Publication Date:	2006-04-13
View Patent Images:	**Login** or **Create Account (Free!)**
Related Patents:	**View patents that cite this patent**
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Assignee:	Altana Pharma AG
Primary Class:	**514/263.34**
Other Classes:	
International Classes:	A61K 31/522 20060101 A61K031/522; A61K 31/513 20060101 A A61K031/473; A61K 31/426 20060101 A61K031/426; A61K 31/2

Foreign Patent References:	**Date**	**Code**	**Application Number**
	Nov 27, 2002	EP	02026548.4

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Claims:

1. A method for treating cachexia, comprising administering to a patient in need t amount of a PDE4 inhibitor or a pharmaceutically acceptable derivative thereof, o pharmaceutically acceptable derivative thereof.

2. The method according to claim 1, whereby the cachexia is a result of cancer, A infections, burns, chronic cardiac insufficiency, cirrhosis of the liver, COPD or chrc

3. The method according to claim 2, wherein the cachexia is a result of cancer.

4. The method according to claim 3, wherein the cancer is selected from the grou cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung cancer, l cancer, thyroid cancer, pancreatic cancer, prostate cancer and bladder cancer.

5. The method as claimed in claim 1, wherein the PDE4 inhibitor or PDE3/4 inhibi

consisting of CDC-998, SH-636, D-4396, SCH-351591, IC-485, CC-1088, KW-44ç methoxybenzyl]-6-(ethylamino)-8-isopropyl-3H-puri- ne [Research-Code: V-112ç 3,4,6,7-tetrahydropyrrolo[3,2,1-jk][1,4]benzo-- diazepin-3(R)-yl]pyridine-4-carb 4-(3,4-dimethoxyphenyl)thiazole-2-carboxamideoxime [Research Code: ORG-20ž 1-propyl-1H-purine-2,6-dione [INN AROFYLLINE], 3-[3-(Cyclopentyloxy)-4-methc methanol, (-)-cis-9-ethoxy-8-methoxy-2-methyl-1,2,3,4,4a, 10b-hexahydro-6-(4 benzo-[c][1,6]naphthy- ridine [INN: PUMAFENTRINE], N-(3,5-dichloro-4-pyridiny 1H-indol-3-y- l]-2-oxoacetamide [Research-Code: AWD-12-281], N-(3,5-dichloro fluorobenzyl)-1H-indol-3-yl-]-2-oxoacetamide [Research-Code: AWD-12-343], 8 xanthine [INN:CIPAMFYLLINE], Tetrahydro-5-[4-methoxy-3-[(1S,2S,4R)-2-norbo [INN: ATIZORAM], .beta.-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1,3-dihydro-1,3 [Research-Code: CDC-801], Methanesulfonic acid 2-(2,4-dichlorophenylcarbonyl) [Research-Code: BAY-19-8004], (Z)-5-(3,5-di-tert-butyl-4-hydroxybenzylidene)- DARBUFELONE], cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan CILOMILAST], 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid-4-y and pharmaceutically acceptable derivatives thereof.

6. The method as claimed in claim 1, wherein the PDE4 inhibitor or PDE3/4 inhibit consisting of (-)-cis-9-ethoxy-8-methoxy-2-methyl-1,2,3,4,4a,10b-hexahydro-6-1 benzo-[c][1,6]naphthyridine [INN: PUMAFENTRINE] 3-Cyclo-propylmethoxy-4-dif yl)-benzam- ide [INN: ROFLUMILAST], and pharmaceutically acceptable derivativ

7. The method as claimed in claim 1, wherein the PDE3/4 inhibitor is (-)-cis-9-eth 1,2,3,4,4a,10b-hexahydro-6-(4-diisopr- opylaminocarbonylphenyl)-benzo-[c][1,6 or a pharmaceutically acceptable derivative thereof.

8. The method as claimed in claim 1, wherein the PDE4 inhibitor is 3-Cyclopropyl dichloropyrid-4-yl)-benzami- de [INN: ROFLUMILAST] or a pharmaceutically acce

9. The method as claimed in claim 8, wherein the PDE4 inhibitor is 3-Cyclopropyl dichloropyrid-4-yl)-benzam- ide [INN: ROFLUMILAST] or a pharmaceutically acce pharmaceutically acceptable N-oxide or a pharmaceutically acceptable salt or solv

10.-12. (canceled)

13. The method according to claim 1, wherein the PDE4 inhibitor or the pharmace or the PDE3/4 inhibitor or the pharmaceutically acceptable derivative thereof is el in the induction of a cachectic symptom.

14. A method for treating cachexia in a human afflicted with cancer comprising th need thereof a therapeutically effective amount of a PDE4 inhibitor or a pharmace or a PDE3/4 inhibitor or a pharmaceutically acceptable derivative thereof.

15. The method according to claim 14, whereby the survival period of a cancer pa

16. A method for improving the response to chemo- and/or radiation-therapy in a cachexia comprising the steps of administering an effective amount of a chemoth an effective amount of a PDE4 inhibitor or a pharmaceutically acceptable derivati pharmaceutically acceptable derivative thereof.

Description:

FIELD OF APPLICATION OF THE INVENTION

[0001] The present invention relates to PDE4 inhibitors and PDE3/4 inhibitors for substances used in accordance with this invention are known active compounds fi inhibitor class.

PRIOR ART

[0002] WO9923076, WO0009504, WO0147914, WO0157036, WO02060898, U.S. 6,313,156, U.S. Pat. No. 5,728,844, EP1229034 list therapeutically active compo as their use for the treatment of numerous diseases.

DESCRIPTION OF THE INVENTION

[0003] Cachexia is a syndrome of wasting associated with many forms of cancer cirrhosis, chronic kidney insufficiency, COPD (chronic obstructive pulmonary disea The clinical picture of cachexia includes weight loss, anorexia (i.e. loss of appetite mass and loss of fat mass, muscle atrophy, gain in the proportion of body-water, Generally, cachexia associated with cancer is not a local effect of a tumor, but is t metabolic effects, i.e. it is a type of paraneoplastic syndrome. Clinical trials direct have failed to reverse the symptoms of cachexia. The pattern of weight loss in ca from normal starvation. The normal adaptive response to nutrient deprivation is t sparing protein, resulting in loss of fat and relative preservation of lean body tissu experience severe and incapacitating muscle wasting with relative sparing of adip

[0004] Undisputedly, there is a medical need for better treatment options of cach from cachexia as a result of cancer. Cachexia is seen in more than 60% of cancer cancer therapy is very often dependent on the presence or absence of cachexia s poorer response to chemo- and radiation therapy are observed in patients with sy Am. J. Med 69: 491-497 (1980); Kern et al., J. Parenter. Enter. Nutr. 12: 286-29 most important contributors that lead to loss of quality of life in cancer patients a mortality.

[0005] In general, two different approaches have been undertaken to manage an Firstly, nutritional supplementation with improved diet or, secondly, drugs to incr patients. But--like megestrol acetate--drugs to increase appetite have generally b acetate only being capable of restoring adipose body weight.

[0006] Although little is known about the precise mechanisms of cachexia, recent production and release of cytokines such as TNF-.alpha., Interleukin-1, Interleuki involved in the induction of cachexia. Knapp et al. (1991) observed elevated TNF advanced stage IV breast cancer patients [Knapp et al., Ann Clin. Biochem., 28: reported that antibodies to TNF could significantly reduce the loss of carcass prot model [Sherry et al., FASEB J. 3: 1956-1962 (1989)]. Fong et al. found that IL-1 LPS as inducers of anorexia and cachexia in rats [Fong et al., Am. J. Physiol. 256: reviewed that further cytokines, e.g. Leukemia Inhibitory Factor (LIF), Ciliary Neu Interferon-.gamma., are associated with cachexia [Mattys and Billiau, Nutrition 1:

[0007] These data indicate that multiple cytokines secreted from tumor and host are able to cause the metabolic changes associated with cachexia and finally to in

[0008] It is the object of the present invention to make available a treatment of c conditions: (1) Suppression or neutralization of cytokines involved in induction of influencing the bioactivity of several and not only of a single cytokine.

[0009] Surprisingly, it has now been found that the use of a PDE4 or a PDE3/4 in conditions.

[0010] In a first embodiment of this invention, there is provided the use of a PDE pharmaceutically acceptable derivative thereof for the manufacture of a pharmac of cachexia.

[0011] According to this invention, "PDE4 inhibitor" refers to a selective phospho inhibits preferentially the type 4 phosphodiesterase (PDE4) when compared to otl e.g. type 1, 2, 3, 5, etc. (PDE1, PDE2, PDE3, PDE5, etc.). According to this invent preferentially inhibiting PDE4 refers to a compound having a lower IC.sub.50 for I inhibition is about 10 times lower than the IC.sub.50 for inhibition of other knowr 1, 2, 3, 5, etc.) and therefore is more potent to inhibit PDE4. Analogously, the te compound having a lower IC50 for the type 3/4 phosphodiesterases and therefor inhibit PDE3/4.

[0012] Methods to determine the activity and selectivity of a phosphodiesterase i skilled in the art. In this connection it may be mentioned, for example, the methc Cycl Nucl Res 10: 69-92, 1979), Giembycz et al. (Br J Pharmacol 118:1945-1958 scintillation proximity assay of Amersham Pharmacia Biotech.

[0013] Possible PDE4 or PDE3/4 inhibitors within the meaning of the present inve inhibitors which are cited expressis verbis as an example, or described or claimed applications and patents: DE 1545687, DE 2028869, DE 2123328, DE 2315801, [

3900233, EP 0103497, EP 0139464, EP 0158380, EP 0163965, EP 0335386, EP 0 0435811, EP 0449216, EP 0459505, EP 0470805, EP 0490823, EP 0506194, EP 0 0553174, EP 0557016, EP 0626939, EP 0664289, EP 0671389, EP 0685474, EP 0 0736532, EP 0738715, EP 0748805, EP 0763534, EP 0816357, EP 0819688, EP 0 0848000, JP 92234389, JP 94329652, JP 95010875, JP 98072415, JP 98147585, 5,739,144, WO 9117991, WO 9200968, WO 9212961, WO 9307146, WO 931504 9319068, WO 9319720, WO 9319747, WO 9319749, WO 9319751, WO 9325517, 9420455, WO 9422852, WO 9427947, WO 9500516, WO 9501338, WO 9501980, 9504046, WO 9505386, WO 9508534, WO 9509623, WO 9509624, WO 9509627, 9514680, WO 9514681, WO 9517392, WO 9517399, WO 9519362, WO 9520578, 9527692, WO 9535281, WO 9535283, WO 9535284, WO 9600218, WO 9601825, 9611690, WO 9611917, WO 9612720, WO 9631486, WO 9631487, WO 9635683, 9636611, WO 9636625, WO 9636626, WO 9636638, WO 9638150, WO 9639408, 9704779, WO 9705105, WO 9708143, WO 9709345, WO 9712895, WO 9718208, 9722585, WO 9722586, WO 9723457, WO 9723460, WO 9723461, WO 9724117, 9728131, WO 9730999, WO 9731000, WO 9732853, WO 9735854, WO 9736905, 9744036, WO 9744322, WO 9747604, WO 9748697, WO 9804534, WO 9805327, 9807715, WO 9808828, WO 9808830, WO 9808841, WO 9808844, WO 9809946, 9814448, WO 9818796, WO 9821207, WO 9821208, WO 9821209, WO 9822453, 9845268, WO 9855481, WO 9856756, WO 9905111, WO 9905112, WO 9505113, 9931071, WO 9931090, WO 9947505, WO 9957115, WO 9957118, WO 9964414, 0042017, WO 0042018, WO 0042019, WO 0042020, WO 0042034, WO 0119818, 0151470, WO 0206239, WO 0206270, WO 0205616 and WO 0206238.

[0014] In addition, PDE4 and PDE3/4 inhibitors are exemplary exhibited on the fc formulae:

[0015] In the above cited formulae there is given neither any stereochemical info indicated [--O is accordingly --OH, --N is NH, --N is NH.sub.2. Methyl groups, e.g by lines].

[0016] Furthermore, those PDE4 inhibitors and PDE3/4 inhibitors are preferred w example and/or claimed generically in the patent applications or patents EP 0163 0435811, EP 0482302, EP 0499216, EP 0506194, EP 0510562, EP 0528922, EP 0 WO 9500516, WO 9501338, WO 9600218, WO 9603399, WO 9611690, WO 9636 9728131, WO 9735854, WO 9740032, WO 9743288, WO 9809946, WO 9807715, 9821208, WO 9821209, WO 9822453, WO 9831674, WO 9840382, WO 9855481, 9905113, WO 9931071, WO 9931090, WO 9947505, WO 9957115, WO 9957118, 0012501, WO 0042017, WO 0042018, WO 0042019, WO 0042020, WO 0042034, 0130777, WO0151470, WO 0206239, WO 0206270, WO 0205616 and WO 02062 following research codes: CDC-998, D-4396, SCH-351591, IC-485, CC-1088 and oral availability are preferred here.

[0017] More particularly preferred PDE4 inhibitors or PDE3/4 inhibitors are the co CDC-998, SH-636, D-4396, SCH-351591, IC-485, CC-1088, KW-4490 and 3-[3-((ethylamino)-8-isopropyl-3H-puri- ne [Research-Code: V-11294A], N-[9-methyl- tetrahydropyrrolo[3,2,1 jk][1,4]benzo-diazepin-3(R)-yl]pyridine-4-carboxamide [dimethoxyphenyl)thiazole-2-carboxamideoxime [Research Code: ORG-20241], 3, propyl-1H-purine-2,6-dione [INN AROFYLLINE], 3-[3-(Cyclopentyloxy)-4-methox methanol, (-)-cis-9-ethoxy-8-methoxy-2-methyl-1,2,3,4,4a, 10b-hexahydro-6-(4 benzo-[c][1,6]naphthyr- idine [INN: PUMAFENTRINE], N-(3,5-dichloro-4-pyridiny 1H-indol-3-y- l]-2-oxoacetamide [Research-Code: AWD-12-281], N-(3,5-dichloro fluorobenzyl)-1H-indol-3-yl-]-2-oxoacetamide [Research-Code: AWD-12-343], 8 xanthine [INN:CIPAMFYLLINE], Tetrahydro-5-[4-methoxy-3-[(1S,2S,4R)-2-norbo [INN: ATIZORAM], .gamma.-[3-(Cyclopentyloxy)-4-methoxyphenyl]-1,3-dihydro- propanamide [Research-Code: CDC-801], Methanesulfonic acid 2-(2,4-dichloroph yl ester [Research-Code: BAY-19-8004], (Z)-5-(3,5-di-tertbutyl-4-hydroxybenzyl [INN: DARBUFELONE], cis-[4-Cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclo CILOMILAST] and 3-Cyclopropylmethoxy-4-difluoromethoxy-N-(3,5-dichloropyrid ROFLUMILAST].

[0018] Most particularly preferred PDE4 inhibitors or PDE3/4 inhibitors are 3-Cycl N-(3,5-dichloropyrid-4-yl)-benzamide [INN: ROFLUMILAST] and (-)-cis-9-ethoxy- hexahydro-6-(4-diisopropylaminocarbonylphenyl)-benzo-[c][1,6]naphthyr- idine | inhibitor N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy-4-difluoromethoxybenz N-oxide is described in WO95/01338.

[0019] In a further embodiment of this invention, there is provided the use of (-) 1,2,3,4,4a, 10b-hexahydro-6-(4-diisopropylaminocarbonylphenyl)-benzo-[c][1,6] PUMAFENTRINE] or a pharmaceutically acceptable derivative thereof for the mani composition for the treatment of cachexia.

[0020] In a further embodiment of this invention, there is provided the use of 3-(difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-- benzamide [INN: ROFLUMILAST] or derivative thereof for the manufacture of a pharmaceutical composition for the tr

[0021] In the context of the present invention, unless otherwise stated, a pharm active ingredient means a pharmaceutically acceptable salt or solvate (e.g. hydra solvate of such salt, a pharmaceutically acceptable N-oxide or a pharmaceutically latter.

[0022] According to this invention, suitable pharmaceutically acceptable salts refe acid addition salts with acids such as, for example, hydrochloric acid, hydrobromi sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybe sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-napl in salt preparation depending on whether it is a mono- or polybasic acid and depe equimolar quantitative ratio or one differing therefrom. Furthermore, the active c present as pure enantiomers or as enantiomer mixtures in any mixing ratio.

[0023] In addition, suitable pharmaceutically acceptable salts also refer to salts w sodium, potassium) or calcium, aluminium, magnesium, titanium, ammonium, m also employ bases in salt preparations in an equimolar quantitative ratio or devia

[0024] PDE4 inhibitors and PDE3/4 inhibitors used in the present invention are ca forms. The invention encompasses all stereoisomers of PDE4 inhibitors and PDE3, including racemates. Tautomers of PDE4 inhibitors and PDE3/4 inhibitors and mix present invention.

[0025] In a further embodiment of this invention, there is provided the use of 3-(difluoromethoxy-N-(3,5-dichloropyrid-4-yl)-- benzamide [INN: ROFLUMILAST] or solvate (e.g. hydrate) thereof, or a pharmaceutically acceptable solvate of such s N-oxide thereof or a pharmaceutically acceptable salt or solvate of the latter for t composition for the treatment of cachexia.

[0026] According to this invention, treatment refers to the administration of a PD pharmaceutically acceptable derivative thereof in a human, whereby the activity (inhibitor or pharmaceutically acceptable derivative thereof results in suppression in induction of cachectic symptoms or in influencing the bioactivity of several cytc treatment also refers to prophylaxis which itself refers to measures designed to p dissemination.

[0027] In a further embodiment of this invention, there is provided the use of a P pharmaceutically acceptable derivative thereof for the manufacture of a pharmac of cachexia as a result of cancer, chronic cardiac insufficiency, cirrhosis of the live and chronic infections, burns, COPD, chronic kidney insufficiency, malaria, hypopl or Addison's disease.

[0028] In particular, the use of a PDE4 inhibitor or a PDE3/4 inhibitor or a pharm thereof for the manufacture of a pharmaceutical composition for the treatment of preferred.

[0029] According to this invention, cancer refers to a cancer selected from the gr ovarian cancer, stomach cancer, endometrial cancer, salivary gland cancer, lung (colorectal cancer, thyroid cancer, pancreatic cancer, prostate cancer and bladder

[0030] In a further embodiment of this invention, there is provided the use of a P a pharmaceutically acceptable derivative thereof for the manufacture of a pharm suppression of cytokines involved in the induction of a cachectic symptom.

[0031] According to this invention, suppression of cytokines refers to decreasing cytokines (i.e. TNF-.alpha., IL-1, IL-6, IFN-.gamma., LIF or CNTF) in patients suf

concentration of said cytokines measurable in healthy humans.

[0032] In accordance with this invention, a cachectic symptom refers to a sympt of weight loss, anorexia, loss of protein mass, loss of fat mass, muscle atrophy ar water.

[0033] In accordance with this invention, PDE4 inhibitors or PDE3/4 inhibitors or derivatives thereof are used for the preparation of a pharmaceutical composition. may be part of a pharmaceutical composition, a pharmaceutical product or a prep admixture with one or more pharmaceutically acceptable auxiliaries and/or excipi

[0034] The person skilled in the art is familiar with pharmaceutical compositions, preparations and therefore, on the basis of his/her expert knowledge, the person excipients or auxiliaries are suitable for the desired pharmaceutical composition, p preparation. In addition to solvents, gel-forming agents, tablet excipients and oth person skilled in the art knows to use, for example, antioxidants, dispersants, em corrigents, preservatives, solubilizers, colorants or permeation promoters and cor

[0035] According to the present invention, a pharmaceutical composition compris inhibitor for the treatment of cachexia is administered orally, parenterally, intrave particular, oral administration and intravenous administration are preferred.

[0036] In case of a pharmaceutical composition (the term "pharmaceutical comp pharmaceutical preparation), which is intended for oral administration, the therap medicament according to processes known per se and familiar to the person skille employed as medicament, preferably in combination with suitable pharmaceutical coated tablets, capsules, emulsions, suspensions or solutions, whereby the PDE4 advantageously is between 0.1 and 95%, preferably between 1 and 80%, particu By appropriate choice of the excipients and the auxiliaries it is possible to achieve precisely tailored to the active ingredient(s) and/or to the desired onset of action enteric form).

[0037] Injectable preparations, for example, sterile injectable aqueous or oleagin formulated according to the known art using suitable dispersing or wetting agents injectable preparation can also be a sterile injectable solution or suspension in a r or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable ve employed are water, Ringer's solution, and isotonic sodium chloride solution. In a conventionally employed as a solvent or suspending medium. For this purpose an including synthetic mono- or diglycerides. Furthermore, fatty acids, such as oleic injectables. Dimethyl acetamide, surfactants including ionic and non-ionic deterge

[0038] In general, satisfactory results will be obtained when the total daily dosag inhibitors, when taken oral or intravenous is in the range from 1-2000 .mu.g/kg c particularly preferred PDE4 inhibitor ROFLUMILAST, the daily dosage is in a range The daily dosage for the particularly preferred PDE3/4 inhibitor PUMAFENTRINE is of body weight.

[0039] In case of oral administration of 3-cyclopropylmethoxy-4-difluoromethoxy de (ROFLUMILAST), the adult daily dose is in the range from 50-1000 .mu.g, pref 500 .mu.g, preferably by once daily administration.

[0040] In case of intravenous administration of 3-cyclopropylmethoxy-4-difluoror benzamid- e (ROFLUMILAST), the adult daily dose is in the range from 50-600 .m 300 .mu.g.

[0041] In a further embodiment of this invention, there is provided the use of a P a pharmaceutically acceptable derivative thereof for the manufacture of a pharma survival period of a cancer patient afflicted to cachexia.

[0042] In an further embodiment of this invention, there is provided a method fo cachexia characterized by administration of a pharmaceutical composition compri inhibitor or a pharmaceutically acceptable derivative thereof.

[0043] In a further embodiment of this invention, there is provided a method for characterized by administration of a pharmaceutical composition comprising a PD pharmaceutically acceptable derivative thereof, whereby cachexia is a result of ca

acute and chronic infections, burns, chronic cardiac insufficiency, cirrhosis of the l insufficiency.

[0044] In a further embodiment of this invention, there is provided a method for characterized by administration of a pharmaceutical composition comprising a PD pharmaceutically acceptable derivative thereof, whereby the PDE4 inhibitor or the pharmaceutically acceptable derivative thereof is effective to suppress cytokines i symptom.

[0045] In a further embodiment of this invention, there is provided a method for afflicted to cancer comprising the step of administering an effective amount of a f a pharmaceutically acceptable derivative thereof.

[0046] In a further embodiment of this invention, there is provided a method for afflicted to cancer comprising the step of administering an effective amount of a f a pharmaceutically acceptable derivative thereof, whereby the survival period of a enlarged.

[0047] In a further embodiment of this invention, there is provided a method for and/or radiation-therapy in a human afflicted to cancer and cachexia comprising t amount of a chemotherapeutic agent and/or radiation and an effective amount of or a pharmaceutically acceptable derivative thereof.

[0048] According to this invention, improving the response to chemo- and/or rad cancer and cachexia refers to prolonging the survival period of said human. In pa interval of time a human afflicted to cancer and cachexia survives after having ch

[0049] According to this invention, a PDE4 inhibitor or a PDE3/4 inhibitor or a pha thereof may be administered before, during and/or after radiation. It may be alsc during and after, before and after, or before, during and after radiation.

[0050] According to this invention, the source of radiation can be external or inte is administered in accordance with known techniques known to a person skilled ir radiation therapy or brachytherapy, i.e. a therapy carried out by placing the sour of radiation depends on numerous factors as is well known in the art. Such factor healthy organs in the path of the radiation that might be adversely affected, the t therapy, and the area of the body in need of treatment. The dose will typically be particular between 2 and 80 Gy.

[0051] According to this invention, chemotherapy refers to treatment with a cher accordance with this invention, a PDE4 inhibitor or a PDE3/4 inhibitor or a pharm thereof may be administered before, during, after, before and during, during and during and after treatment with a chemotherapeutic agent.

[0052] According to this invention, chemotherapeutic agent is a chemotherapeuti consisting 5 FU, actinomycin D, ABARELIX, ABCIXIMAB, ACLARUBICIN, ADAPALEI AMINOGLUTETHIMIDE, AMIPRILOSE, AMRUBICIN, ANASTROZOLE, ANCITABINE, BASILIXIMAB, BENDAMUSTINE, BICALUTAMIDE, BLEOMYCIN, BROXURIDINE, BU CARBOPLATIN, CARBOQUONE, CARMUSTINE, CETRORELIX, CHLORAMBUCIL, CHL CLADRIBINE, CLOMIFENE, CYCLOPHOSPHAMIDE, DACARBAZINE, DACLIZUMAB, DESLORELIN, DEXRAZOXANE, DOCETAXEL, DOXIFLURIDINE, DOXORUBICIN, DR EDELFOSINE, EFLORNITHINE, EMITEFUR, EPIRUBICIN, EPITIOSTANOL, EPTAPLAT ETOPOSIDE, EXEMESTANE, FADROZOLE, FINASTERIDE, FLOXURIDINE, FLUCYTO FLUTAMIDE, FORMESTANE, FOSCARNET, FOSFESTROL, FOTEMUSTINE, FULVESTF GLIVEC, GOSERELIN, GUSPERIMUS, HERCEPTIN, IDARUBICIN, IDOXURIDINE, IF INFLIXIMAB, IRINOTECAN, LANREOTIDE, LETROZOLE, LEUPRORELIN, LOBAPLATI MERCAPTOPURINE, METHOTREXATE, METUREDEPA, MIBOPLATIN, MIFEPRISTONE MITOGUAZONE, MITOLACTOL, MITOMYCIN, MITOXANTRONE, MIZORIBINE, MOTE NEBAZUMAB, NEDAPLATIN, NILUTAMIDE, NIMUSTINE, OCTREOTIDE, ORMELOXIF PALIVIZUMAB, PEGASPARGASE, PEGFILGRASTIM, PENTETREOTIDE, PENTOSTATI PIRARUBICIN, PLICAMYCIN, PREDNIMUSTINE, PROCARBAZINE, PROPAGERMANIU RALTITREXED, RANIMUSTINE, RANPIRNASE, RASBURICASE, RAZOXANE, RITUXII ROMURTIDE, RUBOXISTAURIN, SARGRAMOSTIM, SATRAPLATIN, SIROLIMUS, SO STREPTOZOCIN, TAMOXIFEN, TASONERMIN, TEGAFUR, TEMOPORFIN, TEMOZOLC THIOTEPA, THYMALFASIN, TIAMIPRINE, TOPOTECAN, TOREMIFENE, TRASTUZUM. TRIMETREXATE, TRIPTORELIN, TROFOSFAMIDE, UREDEPA, VALRUBICIN, VERTEP

VINDESINE, VINORELBINE and VOROZOLE.

FIGURES

[0053] FIG. 1: Effects of Zardaverine (left graph) and Piclamilast (right graph) or lung adenocarcinoma Xenograft explants. Tumor fragments from mice carrying L cell suspensions were seeded into 24 Well plates. After seeding of the cells, Zard and 0.1 .mu.M, respectively, and Piclamilast at concentrations of 1, 0.3 and 0.00 supernatants were harvested 24 hours later. IL-1 content of the supernatants wa ELISA kits according to the manufacturer's recommendations. Zardaverine (left g secretion of IL-1 from 85.3 pg/ml in control supernatants (treated with the respe and 77.1 pg/ml at concentrations of 100, 3, and 0.1 .mu.M, respectively. Piclamil the secretion of IL-1 from 85.3 pg/ml in control supernatants (treated with the re 64.4, and 81.9 pg/ml at concentrations of 1; 0.3, and 0.001 .mu.M, respectively.

[0054] FIG. 2: Effects of Zardaverine (left graph) and Piclamilast (right graph) or hypernephroma Xenograft explants. Tumor fragments from mice carrying RXF 39 suspensions were seeded into 24 Well plates. After seeding of the cells, Zardaveri 0.1 .mu.M, respectively, and Piclamilast at concentrations of 1, 0.01 and 0.001 .r supernatants were harvested 24 hours later. IL-1 content of the supernatants wa ELISA kits according to the manufacturer's recommendations. Zardaverine (left g secretion of IL-1 from 46.9 pg/ml in control supernatants (treated with the respe 48.1 pg/ml at concentrations of 100 and 0.1 .mu.M, respectively. Piclamilast (rig secretion of IL-1 from 46.9 pg/ml in control supernatants (treated with the respe and 43.2 pg/ml at concentrations of 1; 0.01, and 0.001 .mu.M, respectively.

[0055] FIG. 3: Effects of Zardaverine (left graph) and Piclamilast (right graph) or LXFA 526 lung adenocarcinoma Xenograft explants. Tumor fragments from mice excised and cell suspensions were seeded into 24 Well plates. After seeding of th of 100, 3, and 0.1 .mu.M, respectively, and Piclamilast at concentrations of 1, 0.3 added and supernatants were harvested 24 hours later. TNF.alpha. content of the R&D Quantikine ELISA kits according to the manufacturer's recommendations. Za suppress the secretion of TNF.alpha. from 16.8 pg/ml in control supernatants (tre DMSO) to 12.6; 12.9, and 13.8 pg/ml at concentrations of 100, 3, and 0.1 .mu.M graph) was able to suppress the secretion of IL-1 from 16.8 pg/ml in control supe amount of DMSO) to 13.9; 15.1, and 17.2 pg/ml at concentrations of 1; 0.3, and

[0056] FIG. 4: Effects of Zardaverine (left graph) and Piclamilast (right graph) or LXFE 397 epidermoid adenocarcinoma Xenograft explants. Tumor fragments from were excised and cell suspensions were seeded into 24 Well plates. After seeding concentrations of 30, 10, and 3 .mu.M, respectively, and Piclamilast at concentrat respectively were added and supernatants were harvested 24 hours later. TNF.alp quantitated using R&D Quantikine ELISA kits according to the manufacturers recc graph) was able to suppress the secretion of TNF.alpha. from 30.3 pg/ml in contr respective amount of DMSO) to 20.1; 28.2, and 27.7 pg/ml at concentrations of 3 Piclamilast (right graph) was able to suppress the secretion of TNF.alpha. from 21 (treated with the respective amount of DMSO) to 10; 12.1, and 14.1 pg/ml at cor 0.03 .mu.M, respectively.

EXAMPLE

[0057] Effectiveness of PDE3/4 and PDE4 inhibitors in the suppression of cytokine cachexia.

[0058] The PDE3/4 inhibitors Zardaverine and PDE4 inhibitor Piclamilast were util the suitability of PDE4 and/or PDE3/4 inhibitors in the suppression of cachexia-in

[0059] To this end primary cultures of tumor cells were derived from cachexia inc subcutaneously in nude mice. The xenograft cell derivatives and their measurable in Table 1. TABLE-US-00001 TABLE 1 TNF.alpha. Tumor Histology IL-1 comment PXC adenocarcinoma (lung) + + LXFE397 epidermoid not detectable +

[0060] 5 to 10 NMRI nude mice were implanted with tumor fragments derived frc and grown until the tumors reached approximately 0.5 g, which correlated well w were then sacrificed and tumors were excised. Cells were subsequently isolated u mechanic disintegrators, proteases, hyaluronidase, and DNAse I. The crude suspe

sterile sieves with diameters of 200 and 50 .mu.M, respectively.

[0061] Washed cell pellets were resuspended in Iscove's modified Dulbecco's Mec 0.24 to 1.times.10.sup.6 tumor cells were seeded in 24 well plates. The cell isolat also blood cells and stromal elements of murine origin. The cell lines RXF 486L wa 1.times.10.sup.6 cells were seeded into each well.

[0062] Piclamilast and Zardaverine were dissolved in 100% DMSO (dimethyl sulfc concentration of 1 .mu.M to 0.001 .mu.M (Piclamilast) or 100 .mu.M to 0.1 .mu.M plated at the same time. 24 hours after seeding supernatants were collected, cen

[0063] For the quantitative measurement of IL-1, IL-6, and TNF.alpha., respectiv using Quantikine ELISA Kits from R&D Systems according to the manufacturer's r

[0064] Modulation of IL-1 expression was investigated in two cell systems: LXFA and Piclamilast were in both cell lines able to suppress IL-1 levels with Zardaverir Piclamilast (results are shown in FIGS. 1 and 2).

[0065] The modulation of TNF.alpha. levels by Zardaverine and Piclamilast was ir the LXFE 397 model, as shown in FIGS. 3 and 4. In both cell systems, Zardaverin the secretion of TNF.alpha. by the respective cell isolates into the medium.

[0066] These data show that PDE4 as well as PDE 3/4 inhibitors have the potenti cytokines linked to cachexia from tumor cell isolates that originate from cachexia noted that COX-2 inhibitors that to some extent exert anti-cachectic activity depe investigated, were unable in this system to suppress the secretion of either IL-1 c in the above described system.

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